5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☐ claims Nos.

   because:

   ☒ the said international application, or the said claims Nos. 88-162 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-166,177
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-166,177
Industrial applicability (IA)	Yes:	Claims	1-87,163-166,177
	No:	Claims	88-162

2. Citations and explanations

see separate sheet

I. Basis

I.1 The amendments filed with the letter dated 17.12.2004 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

In claim 1 was introduced the expression "wherein the hydrophobic moiety...with better (I) membrane permeability **and/or** (b) interaction...patch of the GSK-3". It should be noted that page 26 last paragraph and page 27 first paragraph rather state "high inhibitory activity of the conjugates...derived from **both**, the replacement... **and** the incorporation of the hydrophobic moiety/moieties, which provides for a better membrane permeability ...**as well as** for a better interaction...".

At pages 7, 14, 15 and 23 of the description and claims 10, 41, 58, 83, 113, 123, 137, 144 and 158 the term **X3** has been replaced by **Y3**. The Applicant should know that the priority document does not serve as basis for amendments.

Claims 5, 36, 53, 78, 108, 132, 153 the expression "at least one" has been substituted by "at least five". Nowhere in the description could be found a basis for said amendment. The same objection applies to the new claims 167-176.

Claim 178 has no basis on the application as originally filed.

III. Non-establishment of Opinion.

III.1 Independent claims 88, 118 and 142 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims and related dependent claims (Article 34(4)(a)(I) PCT).

The patentability can also be dependent upon the formulation of the claims. The EPO, for example, **does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment**, but may allow, however, claims to **a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.**

The reformulation of independent claims 88, 118 and 142 and new dependent claims 175 and 176 do not fall within any of these formulations.

V. Reasoned statement.

This international preliminary examination report is drafted as if the amendments haven't been done except for claim 177 (see item I above).

V.1 Reference is made to the following documents:

D1: WO 01/49709 A (ELDAR FINKLEMAN HAGIT ;UNIV RAMOT (IL); MCINNIS PATRICIA A (US)) 12 July 2001 (2001-07-12)

D2: WO 02/24941 A (UNIV DUNDEE ;BIONDI RICARDO (GB); FRAME SHEELAGH (GB)) 28 March 2002 (2002-03-28)

D3: OELRICHS P B ET AL: 'UNIQUE TOXIC PEPTIDES ISOLATED FROM SAWFLY LARVAE IN THREE CONTINENTS' TOXICON, ELMSFORD, NY, US, vol. 37, no. 3, 1999, pages 537-544, XP000994829 ISSN: 0041-0101

D4: ELDAR-FINKELMAN H ET AL: 'The insulin mimetic action of glycogen synthase kinase-3 inhibitors' DIABETOLOGIA, vol. 45, no. Supplement 2, August 2002 (2002-08), page A 70 XP009031166 38th Annual Meeting of the European Association for the Study of Diabetes (EASD);Budapest, Hungary; September 01-05, 2002 ISSN: 0012-186X

D5: PLOTKIN BATYA ET AL: 'Insulin mimetic action of synthetic phosphorylated peptide inhibitors of glycogen synthase kinase-3.' JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 305, no. 3, June 2003 (2003-06), pages 974-980, XP009031218 ISSN: 0022-3565

D1 and D2 disclose compounds with the sequence motif ZXXXS(p) which inhibit GSK3.

D2 discloses compounds with the sequence motif ZXXXS(p) which inhibit GSK3.

D3 discloses a peptide comprising the sequence ZXXXS(p).

D4 suggests the inhibition of GSK3 by a novel class of peptides. In view of D5, which is a post publication of the present abstract it appears that peptides with SEQ ID No16 were known at the present priority date of 12.12.02.

V.2 Novelty, inventive step and industrial applicability (Art. 33 PCT).

2.1 The present invention concerns conjugates for inhibiting Glycogen Synthase Kinase 3 (GSK3) comprising a) the a sequence comprising the motif ZX1X2X3S(p) where Z is any amino acid except serine or threonine (preferably alanine) and b) an hydrophobic moiety (can be a peptide sequence of minimum 1 amino acid (!) or a fatty acid) attached to the C- or N-terminus of the peptide.

2.3 In view of the prior art documents D1-D4 the subject matter in claims 1-166 and 177 is neither novel nor inventive.
It should be noted that it is obvious that hydrophobic amino acid sequences attached to a functional domain can provide molecules with increased membrane permeability.

2.4 The subject matter in claims 88-162 is not industrial applicable (Art. 33(4) PCT).

V.3 In view of the disclosure in the examples it appears that the peptide defined by SEQ ID No 16 bound to myristic acid would be inventive if document D4 is proved to be irrelevant.

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According to still further features in the described preferred embodiments, X_3 is any amino acid residue except a glutamic acid residue, Z is an alanine residue, and/or n is an integer from 1 to 15, preferably from 1 to 10.

In a preferred embodiment of the present invention, the conjugate has the amino acid sequence set forth in SEQ ID NO:16.

According to another aspect of the present invention there is provided a method of inhibiting an activity of GSK-3, which comprises contacting cells expressing GSK-3 with an effective amount of the conjugate described hereinabove.

The activity can be a phosphorylation activity and/or an autophosphorylation activity. Contacting the cells can be effected *in vitro* or *in vivo*.

According to further features in preferred embodiments of the invention described below, the method further comprises contacting the cells with at least one an additional active ingredient that is capable of altering an activity of GSK-3.

The additional active ingredient can be insulin or any active ingredient that is capable of inhibiting an activity of GSK-3, such as, but not limited to, lithium, valproic acid and a lithium ion.

Alternatively, the additional active ingredient can be an active ingredient that is capable of downregulating an expression of GSK-3, such as a polynucleotide, and more preferably a small interfering polynucleotide molecule directed to cause intracellular GSK-3 mRNA degradation.

The small interfering polynucleotide molecule can be selected from the group consisting of an RNAi molecule, an anti-sense molecule, a rybozyme molecule and a DNAzyme molecule.

According to yet another aspect of the present invention there is provided a method of potentiating insulin signaling, which comprises contacting insulin responsive cells, *in vitro* or *in vivo*, with an effective amount of the conjugate of the present invention, described hereinabove.

According to further features in preferred embodiments of the invention described below, the method further comprises contacting the cells contacting the cells with insulin.

According to still another aspect of the present invention there is provided a method of treating a biological condition associated with GSK-3 activity, which

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-66	as originally filed

Claims, Numbers

1-166	as originally filed
177	received on 20.12.2004 with letter of 17.12.2004

Drawings, Sheets

1/6-6/6	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☒ contained in the international application in written form.
   - ☒ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

TENT COOPERATION TREAT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

08 JUN 2005

Applicant's or agent's file reference F-12643/PCT-SS	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL 03/01057	International filing date (day/month/year) 11.12.2003	Priority date (day/month/year) 12.12.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/47		
Applicant TEL AVIV UNIVERSITY FUTURE TECHNOLOGY ... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 25 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.06.2004	20.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Pinheiro Vieira, E Telephone No. +49 89 2399-7865

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

The present invention is based on the concept that relatively short peptides, derived from the recognition motif of GSK-3, may serve as enzyme inhibitors. This concept, in turn, is based on the findings that GSK-3 has a unique recognition motif and therefore short peptides which are designed with reference to this motif are highly specific GSK-3 inhibitors, as is widely taught in WO 01/49709 and in U.S. Patent Application No. 20020147146A1, which are incorporated by reference as if fully set forth herein.

The unique recognition motif of GSK-3, set forth in SEQ ID NO:19, is $SX_1X_2X_3S(p)$, where S is serine or threonine, each of X_1, X_2 and X_3 is any amino acid, and S(p) is phosphorylated serine or phosphorylated threonine. Based on this recognition motif, a set of peptides, which differ one from another in various parameters (e.g., length, phosphorylation, sequence, etc.) have been designed, synthesized and were tested for their activity as either substrates or inhibitors of GSK-3 (see, for example, Table 3 and the accompanying description in the Examples section that follows).

Based on these experiments, a number of features, which would render a peptide an efficient GSK-3 inhibitor, have been determined. For example, it was found that the phosphorylated serine or threonine residue in the motif is necessary for binding. Without this residue, the peptide will neither be a substrate nor an inhibitor. It was further determined that a serine (or threonine) residue upstream of the phosphorylated serine (or threonine) residue separated by three additional residues renders the peptide a GSK-3 substrate, whereas replacement of this serine or threonine residue by any other amino acid, preferably alanine, converts the substrate to a GSK-3 inhibitor. The nature of the three amino acids (denoted as $X_1X_2X_3$ in the sequence above) was also found to affect the inhibition activity of the peptide, as is detailed hereinafter in the Examples section. In one particular, in was found that the presence of glutamic acid as the X_3 residue, which is detected in many GSK-3

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substrates, reduces the inhibition activity of the peptide and therefore it is preferable to have any amino acid other than glutamic acid at the Y_3 position. It was further found that the number of the additional residues, outside the recognition motif, affect the inhibition potency of the peptide, such that, for example, a total number of between 7 and 50, preferably, between 7 and 20, more preferably between 10 and 13 amino acid residues, is preferable.

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Hence, as is further described and exemplified in the Examples section that follows, it was found that polypeptides having the amino acid sequence:

$$[Yn\text{-}\text{-}\text{-}Y_1]ZX_1X_2X_3S(p)[W_1\text{-}\text{-}\text{-}Wm]$$

wherein m equals 1 or 2; n is an integer from 1 to 50; S(p) is a phosphorylated serine residue or a phosphorylated threonine residue; Z is any amino acid residue excepting serine residue or threonine residue; and X_1, X_2, X_3, Y_1-Yn and W_1-Wm are each independently any amino acid residue, are highly efficient and specific inhibitors of GSK-3.

It was further found that preferred polypeptides are those having an alanine residue at the Z position, having any amino acid residue excepting glutamic acid as X_3, and/or having between 7 and 20 amino acid residues, preferably between 10 and 13 amino acid residues and more preferably between 10 and 11 amino acid residues, such that n equals 1-15, preferably 1-10.

The efficacy and specificity of these polypeptide inhibitors have been successfully demonstrated so far in *in vitro* tests. However, while aiming at evaluating the efficacy of these inhibitors in *in vivo* tests, it was hypothesized by the present inventor that attaching to the polypeptides described above a hydrophobic moiety would enhance their membrane permeability. While reducing this hypothesis to practice, it was surprisingly found, in both *in vitro* and *in vivo* tests, that a conjugate of the polypeptide inhibitor described above and a fatty acid, as a hydrophobic moiety, attached at the N-terminus of the polypeptide, exerts higher inhibition of GSK-3 activity than a corresponding polypeptide devoid of a hydrophobic moiety.

the present invention can have a stabilizing group at one or both termini. Typical stabilizing groups include amido, acetyl, benzyl, phenyl, tosyl, alkoxycarbonyl, alkyl carbonyl, benzyloxycarbonyl and the like end group modifications. Additional modifications include using a "L" amino acid in place of a "D" amino acid at the termini, cyclization of the peptide inhibitor, and amide rather than amino or carboxy termini to inhibit exopeptidase activity.

The peptides of the present invention may or may not be glycosylated. The peptides are not glycosylated, for example, when produced directly by peptide synthesis techniques or are produced in a prokaryotic cell transformed with a recombinant polynucleotide. Eukaryotically-produced peptide molecules are typically glycosylated.

Non-limiting examples of peptides in accordance with the present invention include those that maintain the sequence of a known GSK-3 substrate except for the substitution of the serine or threonine that is at the fourth position upstream of the phosphorylated serine or threonine (denoted as Z in the amino acid sequence described above). Preferably, Z is alanine. When the known substrate from which the inhibitor is derived is the CREB protein, the minimum size of the peptide is 10 residues, with the additional three residues all being upstream of the Z. Similarly, when the substrate from which the peptide is derived is heat shock factor-1 (HSF-1, the minimum number of residues in the peptide must be greater than seven. In addition, preferred peptides according to the present invention exclude glutamic acid at the Y_3 position.

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Preferred polypeptides according to the present invention are those having an amino acid sequence as set forth in SEQ ID NO: 5, SEQ ID NO:8 or SEQ ID NO:9.

As used herein the phrase "hydrophobic moiety" refers to any substance or a residue thereof that is characterized by hydrophobicity. As is well accepted in the art, the term "residue" describes a major portion of a substance, which is covalently linked to another substance, herein the polypeptide described hereinabove.

Hence, a hydrophobic moiety according to the present invention is preferably a residue of a hydrophobic substance, and is covalently attached to the polypeptide described hereinabove. However, it would be appreciated that the hydrophobic moieties of the present invention can be attached to the polypeptide via any other

CLAIMS

1. A conjugate comprising:

(a) a polypeptide having the amino acid sequence :

$$[Yn\cdots Y_1]ZX_1X_2X_3S(p)[W_1\cdots Wm]$$

wherein,

m equals 1 or 2;

n is an integer from 1 to 50;

S(p) is a phosphorylated serine residue or a phosphorylated threonine residue;

Z is any amino acid residue excepting serine residue or threonine residue; and

X_1, X_2, X_3, Y_1-Yn and W_1-Wm are each independently any amino acid residue; and

(b) at least one hydrophobic moiety being attached to said polypeptide,

the conjugate being capable of inhibiting an activity of glycogen synthase kinase-3 (GSK-3), wherein the hydrophobic moiety provides the conjugate with better (i) membrane permeability and/or (b) interaction with the hydrophobic patch of the GSK-3.

2. The conjugate of claim 1, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

3. The conjugate of claim 1, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

4. The conjugate of claim 1, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

5. The conjugate of claim 4, wherein said hydrophobic peptide sequence comprises at least five amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine

residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

6. The conjugate of claim 1, wherein said at least one hydrophobic moiety comprises a fatty acid.

7. The conjugate of claim 6, wherein said fatty acid is attached to at least one amino acid residue.

8. The conjugate of claim 6, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

9. The conjugate of claim 8, wherein said fatty acid is myristic acid.

10. The conjugate of claim 1, wherein Y_3 is any amino acid residue except a glutamic acid residue.

11. The conjugate of claim 1, wherein Z is an alanine residue.

12. The conjugate of claim 1, wherein n is an integer from 1 to 15.

13. The conjugate of claim 12, wherein n is an integer from 1 to 10.

14. The conjugate of claim 1, having the amino acid sequence set forth in SEQ ID NO:16.

15. A pharmaceutical composition comprising, as an active ingredient, the conjugate of claim 1, and a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 15, packaged in a packaging material and identified in print, on or in said packaging material, for use in the treatment of a biological condition associated with GSK-3 activity.

17. The pharmaceutical composition of claim 16, wherein said biological condition is selected from the group consisting of obesity, non-insulin dependent diabetes mellitus, an insulin-dependent condition, an affective disorder, a neurodegenerative disease or disorder and a psychotic disease or disorder.

18. The pharmaceutical composition of claim 17, wherein said affective disorder is selected from the group consisting of a unipolar disorder and a bipolar disorder.

19. The pharmaceutical composition of claim 18, wherein said unipolar disorder is depression.

20. The pharmaceutical composition of claim 18, wherein said bipolar disorder is manic depression.

21. The pharmaceutical composition of claim 17, wherein said neurodegenerative disorder results from an event selected from the group consisting of cerebral ischemia, stroke, traumatic brain injury and bacterial infection.

22. The pharmaceutical composition of claim 17, wherein said neurodegenerative disorder is a chronic neurodegenerative disorder.

23. The pharmaceutical composition of claim 22, wherein said chronic neurodegenerative disorder results from a disease selected from the group consisting of Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS associated dementia, amyotrophic lateral sclerosis (AML) and multiple sclerosis.

24. The pharmaceutical composition of claim 15, further comprising at least one additional active ingredient that is capable of altering an activity of GSK-3.

25. The pharmaceutical composition of claim 24, wherein said additional active ingredient is insulin.

26. The pharmaceutical composition of claim 24, wherein said additional active ingredient is capable of inhibiting an activity of GSK-3.

27. The pharmaceutical composition of claim 26, wherein said additional active ingredient is selected from the group consisting of a GSK-3 inhibitor, lithium, valproic acid and a lithium ion.

28. The pharmaceutical composition of claim 24, wherein said additional active ingredient is capable of downregulating an expression of GSK-3.

29. The pharmaceutical composition of claim 28, wherein said additional active ingredient is a polynucleotide.

30. The pharmaceutical composition of claim 29, wherein said polynucleotide is a small interfering polynucleotide molecule directed to cause intracellular GSK-3 mRNA degradation.

31. The pharmaceutical composition of claim 30, wherein said small interfering polynucleotide molecule is selected from the group consisting of an RNAi molecule, an anti-sense molecule, a rybozyme molecule and a DNAzyme molecule.

108. The use of claim 107, wherein said hydrophobic peptide sequence comprises at least five amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

109. The use of claim 88, wherein said at least one hydrophobic moiety comprises a fatty acid.

110. The use of claim 109, wherein said fatty acid is attached to at least one amino acid residue.

111. The use of claim 109, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

112. The use of claim 111, wherein said fatty acid is myristic acid.

113. The use of claim 88, wherein Y_3 is any amino acid residue except a glutamic acid residue.

114. The use of claim 88, wherein Z is an alanine residue.

115. The use of claim 88, wherein n is an integer from 1 to 15.

116. The use of claim 115, wherein n is an integer from 1 to 10.

117. The use of claim 88, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.

118. Use of at least one compound that is capable of specifically inhibiting an activity of GSK-3 for the treatment of an affective disorder.

119. The use of claim 118, wherein said affective disorder is selected from the group consisting of a unipolar disorder and bipolar disorder.

120. The use of claim 119, wherein said unipolar disorder is depression.

121. The use of claim 119, wherein said bipolar disorder is manic depression.

122. The use of claim 118, wherein said compound is a polypeptide having the amino acid sequence:

$$[Yn\cdots Y_1]ZX_1X_2X_3S(p)[W_1\cdots Wm]$$

wherein,
m equals 1 or 2;
n is an integer from 1 to 50;
S(p) is a phosphorylated serine residue or a phosphorylated threonine residue;
Z is any amino acid residue excepting serine residue or threonine residue; and
X_1, X_2, X_3, Y_1-Yn and W_1-Wm are each independently any amino acid residue.

123. The use of claim 122, wherein Y_3 is any amino acid residue except a glutamic acid residue.

124. The use of claim 122, wherein Z is an alanine residue.

125. The use of claim 122, wherein n is an integer from 1 to 15.

126. The use of claim 125, wherein n is an integer from 1 to 10.

127. The use of claim 122, wherein said polypeptide has an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO:12.

128. The use of claim 122, wherein said polypeptide further comprises at least one hydrophobic moiety being attached thereto.

129. The use of claim 128, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

130. The use of claim 128, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

131. The use of claim 128, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

132. The use of claim 131, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

133. The use of claim 128, wherein said at least one hydrophobic moiety comprises a fatty acid.

134. The use of claim 133, wherein said fatty acid is attached to at least one amino acid residue.

135. The use of claim 133, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

136. The use of claim 135, wherein said fatty acid is myristic acid.

137. The use of claim 128, wherein Y_3 is any amino acid residue except a glutamic acid residue.

138. The use of claim 128, wherein Z is an alanine residue.

139. The use of claim 128, wherein n is an integer from 1 to 15.

140. The use of claim 139, wherein n is an integer from 1 to 10.

141. The use of claim 128, wherein said compound has the amino acid sequence set forth in SEQ ID NO:16.

142. A use of at least one compound that is capable of specifically inhibiting an activity of GSK-3 for up-regulating a β-catenin level in a hippocampus of a subject.

143. The use of claim 142, wherein said compound is a polypeptide having the amino acid sequence:

$$[Yn\cdots Y_1]ZX_1X_2X_3S(p)[W_1\cdots Wm]$$

wherein,

m equals 1 or 2;

n is an integer from 1 to 50;

S(p) is a phosphorylated serine residue or a phosphorylated threonine residue;

Z is any amino acid residue excepting serine residue or threonine residue; and

X_1, X_2, X_3, Y_1-Yn and W_1-Wm are each independently any amino acid residue.

165. The process of claim 163, wherein said providing of said polypeptide is by recombinantly producing said polypeptide.

166. The process of claim 163, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.

167. The conjugate of claim 4, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

168. The conjugate of claim 4, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a glycine residue, a leucine residue, a valine residue, and a proline residue.

169. The pharmaceutical composition of claim 35, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

170. The pharmaceutical composition of claim 35, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a glycine residue, a leucine residue, a valine residue, and a proline residue.

171. The method of claim 52, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group

consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

172. The method of claim 52, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a glycine residue, a leucine residue, a valine residue, and a proline residue.

173. The method of claim 77, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

174. The method of claim 77, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a glycine residue, a leucine residue, a valine residue, and a proline residue.

175. The use of claim 107, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

176. The use of claim 107, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a glycine residue, a leucine residue, a valine residue, and a proline residue.

177. Use of the conjugate of claim 1 for the preparation of a medicament for the treatment of a biological condition associated with GSK-3 activity.

178. Use of at least one compound that is capable of specifically inhibiting an activity of GSK-3 for the preparation of a medicament for the treatment of an affective disorder.